51. (Amended) A transgenic non-human animal obtainable according to the method of claim 49.

REMARKS

Claim 45-48 have been canceled. Claims 4, 6, 10, 11, 14-16, 18, 19, 24, 26, 27, 29, 32, 34-37, 39, 41-43, 51 have been amended to better align them with U.S. Patent practice. The specification has been amended with this preliminary amendment to incorporate the priority information for this Application and to reduce the number of words in the abstract. A separate copy of the Abstract is provided herewith on a separate sheet. The substitute specification provided herewith has been amended to include headings and to insert sequence listing numbers for U.S. practice. No new matter was added in incorporating the priority claims and headings. A substitute sequence listing has been provided along with a Computer Readable Form of the Sequence Listing.

The undersigned hereby states that the Paper Copy and the Computer Readable Form are identical. No new matter has been added by these amendments. A version to show changes made to the claims accompanies this amendment. Favorable consideration of the remarks provided below is respectfully requested. Should the Examiner have any questions he or she is invited to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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Version to show Changes Made

The first paragraph of the Background of the Invention has been amended to add:

This Application claims priority from PCT Patent Application No. PCT/EP00/06171 filed June 30, 2000 and entitled "Double Transgenic Animals as Models for Neurodegenerative Disease" which claims priority from Great Britain Patent Application No. 9915576.9 filed July 02, 1999 having the same title, both of which are incorporated by reference into this application in their entirety.

The abstract of the invention has been deleted and the following abstract has been added:

The present invention relates to cell and animal models for a disease condition and in particular to an animal model which can function as a model for neurodegenerative diseases, such as Alzheimers.

The claims have been amended as follows:

4. (Amended) A vector according to [any of] claim[s] 1 [to 3] wherein said sequence encoding human Tau is a cDNA sequence.

6. (Amended) A vector according to [any preceding] claim 1 wherein said sequence capable of directing expression of said human Tau protein is a mouse promoter.

10. (Amended) A vector according to [any of] claim[s] 1 [to 9] further comprising two loxP sites flanking either of the sequences of step (a) and (b).

11. (Amended) A vector according to [any of] claim[s] 1 [to 9] further comprising a stop sequence capable of preventing expression of said human Tau protein and which sequence is flanked by two loxP sites capable of undergoing reciprocal conservative DNA recombination in the presence of Cre recombinase with the resulting excision of said stop sequence.

14. (Amended) A vector according to claim 12 [or 13] wherein said human protein is GSK-3β kinase.

15. (Amended) A vector according to [any of] claim[s] 12 [to 14] wherein said nucleic acid sequence in step a) is a cDNA sequence.

16. (Amended) A vector according to [any of] claim[s] 12 [to 15] wherein said sequence capable of directing expression of said protein capable of modulating human Tau protein is a mouse promoter.

18. (Amended) A vector according to [any of] claim[s] 12 [to 16] further comprising two loxP sites flanking either of the sequences of step (a) and (b).

19. (Amended) A vector according to [any of] claim[s] 12 [to 17] further comprising a stop sequence capable of preventing expression of said protein capable of modulating human Tau protein, and which stop sequence is flanked by two loxP sites capable of undergoing reciprocal conservative DNA recombination in the presence of Cre recombinase with the resulting excision of the stop sequence.

24. (Amended) A method of making a transgenic non-human animal comprising the steps of:

(a) introducing into an embryo cell of said animal one or more of a nucleic acid vectors according to [any of] claim[s] 1 [to 19];
(b) introducing the embryo from step (a) into a female animal;
(c) sustaining the female in step (b) until such time as the embryo has sufficiently developed and is borne from the female; and
(d) sustaining the transgenic animal.

26. (Amended) A method according to claim 25 wherein both

[of the] a vector[s] comprising (a) a nucleic acid sequence encoding a human Tau protein;

(b) a sequence capable of directing expression of said human Tau protein in the nervous system of a non-human animal; and

(c) a targeting sequence which facilitates integration of said vector into the genome of said animal so as to prevent expression of equivalent Tau protein or a related or equivalent protein from said animal in favour of said human Tau protein

[encoding said human Tau and said protein capable of modulating human Tau according to claims 1 to 11] and a vector comprising:

(a) a nucleic acid sequence encoding a human protein capable of modulating human Tau protein;

(b) a sequence capable of directing expression of said protein in the nervous system of said animal; and

(c) a targeting sequence capable of facilitating integration of said vector into the genome of said animal optionally at a position corresponding to a sequence in said animal encoding an equivalent of said human protein so as to prevent expression of said equivalent sequence in favour of said human protein capable of modulating human Tau protein

[12 to 19 respectively] are introduced into said stem cell.

27. (Amended) A method according to [any of] claim[s 24 to] 26 wherein said non-human animal is a mammal.

29. (Amended) A method according to claim 24 [or 25], comprising the step of introducing a vector according to [any of] claim[s] 1 [to 11] into a first animal and a vector according to [any of] claim[s] 12 [to 19] into a second animal, crossing said first and second animals and selecting among the progeny those that express both said human Tau and said protein capable of modulating human Tau protein.

32. (Amended) A method according to claim 30 [or 31] wherein said transgenic non-human animal is a mammal.

34. (Amended) A method according to [any of] claim[s] 30 [to 33] wherein said second nucleic acid vector comprises a sequence of nucleotides comprising a region of homology with a sequence encoding an equivalent Tau protein in said animal or with a region flanking or adjacent said sequence so as to facilitate integration of said vector into the genome of said animal by homologous recombination.

35. (Amended) A method of generating a transgenic non-human animal which is a model for Alzheimers disease or related neurodegenerative disorders, comprising the steps of crossing a first transgenic non-human animal comprising a vector according to [any of] claim[s] 1[to 11] in its genome with a second transgenic non-human animal comprising a vector according to [any of] claim[s] 12 [to 19] in its genome selecting among the progeny those that express both human Tau protein and said kinase.

36. (Amended) A method according to claim 35 wherein said nucleic acid vector in said first transgenic animal comprises a vector according to claim 10 [or 11].

37. (Amended) A method according to claim 36 wherein said second transgenic animal comprises a vector according to [any of] claim[s] 12 [to 19].

39. (Amended) A transgenic non-human animal obtainable according to the methods of [any of] claim[s] 24 [to 38].

41. (Amended) A transgenic non-human animal according to claim 40 wherein said sequence in step (a) comprises a vector according to [any of] claim[s] 1 [to 11].

42. (Amended) A transgenic non-human animal according to claim 40 wherein said sequence according to step (b) comprises a vector according to [any of] claim[s] 12 [to 19].

43. (Amended) A method of identifying a compound which modulates human kinase mediated phosphorylation of human Tau protein which method comprises administering a test compound to a non-human animal according to [any of] claim[s] 39 [to 42] expressing both said human Tau protein and said human kinase and monitoring the phosphorylation profile of said Tau protein compared to one of said transgenic animals which has not been administered with the compound.

51. (Amended) A transgenic non-human animal obtainable according to the method of claim 49 [or 50].

ABSTRACT

TRANSGENIC ANIMALS AS MODELS FOR NEURODEGENERATIVE DISEASE

The present invention relates to cell and animal models for a disease condition and in particular to an animal model which can function as a model for neurodegenerative diseases, such as Alzheimers.